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(54) Title: PHARMACEUTICAL SOLUTIONS AND EMULSIONS CONTAINING TAXOL

(57) Abstract

Compositions of matter are provided comprising a pharmaceutically effective amount of taxol or a tumor-active analog thereof solubilized in a pharmaceutically acceptable carrier comprising an oil having a dipole moment of between about 0.5 Debyes and about 2.0 Debyes, and preferably between about 1.6 and about 1.7 Debyes. Oils from marine organisms having an ether lipid as a major component thereof are preferred. Methods of solubilizing taxol or tumor-active taxol analogs in the pharmaceutically acceptable oils of this invention are provided comprising forming a first solution by dissolving taxol in a preliminary solvent such as an anhydrous alcohol, then adding sufficient oil to solubilize said first solution. Taxol-in-oil solutions are used to prepare oil-in-water emulsions and other dosage forms for pharmaceutical use in antitumor therapy by means known to the art using known surfactants.

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PHARMACEUTICAL SOLUTIONS AND EMULSIONS CONTAINING TAXOL

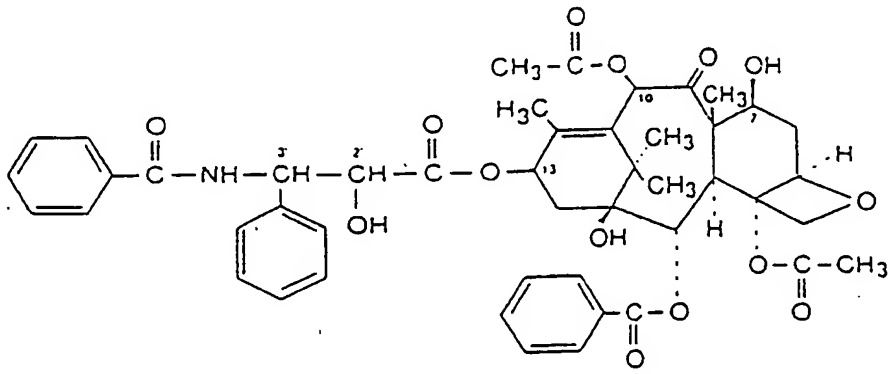
Field of the Invention

This invention is in the field of pharmaceutical compositions, specifically compositions containing the anti-cancer drug, taxol.

Background of the Invention

Taxol is a poorly water soluble alkaloid isolated from several species of Western Yew. Taxol exhibits antimitotic properties and is presently undergoing phase I clinical trials for the treatment of cancers. Taxol has been shown to be active against leukemia, colon, breast, melanoma, sarcomas, and Lewis lung tumor systems. Tarr et al. (1987) Pharm. Res. 4:162-165; Horwitz (1992) TIPS 13:134-136. In vitro studies indicate that concentrations of taxol of 0.1-10.0 μ/ml stabilize microtubules, thus disrupting normal cell division. Rowinsky et al. (1990) J. Natl. Cancer Inst. 82:1247-1259.

Taxol is a complex diterpene having a taxane ring system with a four-membered oxetane ring and an ester sidechain at position C-13, as follows:



In an attempt to increase taxol's solubility and develop more feasible clinical formulations, investigators have acylated carbons at the 7-position and 10-position of the taxene ring. These efforts have yielded compounds that retain anti-tumor activity. Rowinsky et al. (1990) J. Natl. Cancer Inst. 82:1247-1259.

Because of its poor solubility in water and many oils, taxol has been administered in formulations using Cremophors. Cremophors are polyoxyethylated castor oils. The current, most widely used Sigma taxol formulation consists of ethanol:Cremophor EL™:isotonic saline (5:5:90). The drug's solubility in this vehicle does not exceed 0.6 mg/ml and it remains physically stable only for a short time (3 hr). Therefore, in view of the limited solubility, large volumes of these formulations must be infused to obtain a desired total dose of 30 mg. Tarr et al. (1987) Pharm. Res. 4:162-165. A patient is usually required to check into a hospital and endure intravenous infusion for an extended period, such as twenty-four hours. Typically, taxol is administered intravenously in a preparation containing 30 μg/ml over a period of twenty-four hours, followed by a week of rest and another dose. This course of administration is typically repeated two more times.

Further, the BASF Cremophor EL™ (polyoxyethylated castor oil) is extremely toxic and in dogs has been shown to produce vasodilation, labored breathing, lethargy, hypotension and death. Rowinsky et al. (1990) J. Natl. Cancer Inst. 82:1247-1259. Anaphylactoid reactions observed in phase I trials of the taxol formulation in Cremophor EL™ were attributed to the rapid administration of the Cremophor. Grem et al. (1987) Cancer Treat. Rep. 71:1179-1184.

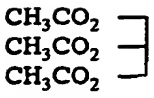
Hypersensitivity reactions have also been observed using the above formulation; one patient had a fatal reaction. It is unclear whether taxol itself or the Cremophor vehicle is

principally responsible for these hypersensitivity reactions. Rowinsky et al. (1990) J. Natl. Cancer Inst. 82:1247-1259.

Water-miscible cosolvents have also been used in taxol preparations but require infusion times even longer than the currently used formulation. Drugs formulated with cosolvents may precipitate if infused too fast. Yalkowsky et al. (1977) Drug Intell. Clin. Pharm. 11:417-419.

To avoid using the toxic Cremophor and provide a non-precipitating I.V. taxol formulation, Tarr et al. (1987) Pharm. Res. 4:162-165 formulated taxol with Intralipid (trademark of RabiVitrum [formerly Cutter Medical]), a commonly used parenteral emulsion comprising soybean oil, lecithin, egg yolk phospholipids, and glycerol. This vehicle was found unsuitable for pharmaceutic use because of the low solubility of taxol in soybean oil (0.3 mg/ml).

Tarr et al. then made taxol emulsion formulations using triacetin, a water-soluble triester. Taxol is soluble in triacetin to a level of about 75 mg/ml. A 50% triacetin emulsion containing 20 mg/ml taxol as well as the emulsifying agents L-alpha-lecithin, pluronic F-86 (BASF), polysorbate 80 (Sigma Chemical Co.), and ethyl oleate was tested as a possible bolus I.V. formulation. Glycerol was added to the triacetin emulsion to slow creaming, but was found to have little effect on emulsion stability. Administration of the 50% triacetin formulation caused toxic reactions including lethargy, ataxia and respiratory depression in animal models, presumably due to the toxicity of the triacetin. The 50% triacetin emulsion showed an intravenous LD50 of 1.2 ml/kg in mice. The triacetin emulsion initially had a 1 μm average diameter particle size which slowly increased and finally exhibited instability, separating into two phases at six months. Vigorous shaking again formed an emulsion having an average droplet size of 2 μm. Triacetin is 1, 2, 3-triacetylglycerol:



As taxol has been determined to be an especially effective anti-cancer agent, formulations which do not contain toxic ingredients and which allow delivery of pharmaceutically relevant dosages in a reasonable period of time, such as orally or by injection, are especially needed. Such formulations have not been previously available.

Methods and compositions for solubilizing pharmaceutically relevant dosages of taxol in pharmaceutically acceptable oils are therefore highly desirable objects of this invention.

The use of oil-in-water emulsions for delivery of taxol and its tumor-active analogs are needed to avoid problems of precipitation of I.V. solutions at the time of administration to increase bioavailability of orally administered taxol and to prevent gastrointestinal upset. In non-emulsified form, taxol is degraded in the stomach. However, prior efforts to produce pharmaceutically acceptable emulsions containing taxol have failed due to both the relative insolubility of taxol in typical pharmaceutically suitable oils and the requirements for toxic surface-active agents.

Pharmaceutically acceptable oils useful in forming oil-in-water emulsions are well-known to the art and include mineral, vegetable, animal and marine oils. However, the low solubility of taxol in many oils, such as safflower, olive and soybean oils (about 0.3-0.6 mg/ml) which have fatty acid glycerides and triglycerides as major components, has prevented the use of such oils in taxol formulations.

Marine oils, especially those that comprise ether lipids rather than ester lipids and terpene hydrocarbons, are known to

the art and include, among many others, orange roughy, squalane, squalene and shark liver oil.

Summary of the Invention

This invention provides compositions of matter comprising a pharmaceutically effective amount of taxol or a tumor-active analog thereof solubilized in a pharmaceutically acceptable carrier comprising an oil having a dipole moment of between about 0.5 Debyes and about 2.0 Debyes, and preferably between about 1.6 and 1.7 Debyes. Oils from deep-water marine organisms are preferred.

Oils comprising ether lipids as major components are preferred. Ether lipids can be glycerol ethers, including unsaturated glycerol ethers and polyunsaturated glycerol ethers. Oils comprising terpene based hydrocarbons derived from marine oils, like squalene and squalane, are also preferred for preparation of taxol solutions.

The compositions of the present invention show a many-fold increase (up to five hundred times) of oral absorption over the prior art formulation using the EL Cremophor™ (BASF).

This invention provides high concentration solutions of taxol or tumor-active taxol analogs in oils having greater than or equal to about 1 mg/ml of taxol dissolved therein. These taxol solutions are useful in the preparation of pharmaceutical emulsions and other dosage forms. Marine oils are preferred taxol solvents, particularly those oils comprising ether lipids including unsaturated and polyunsaturated glycerol ethers. High concentration taxol solutions can also be prepared with oils comprising terpene-based hydrocarbons, like squalane and squalene.

Non-toxic derivatives of squalene and squalane that have dipole moments between about 0.5 Debyes and 2.0 Debyes are also

useful in preparation of high concentration taxol solutions and pharmaceutical dosage forms for taxol.

Solutions of taxol or tumor-active taxol analogs in the pharmaceutically acceptable oils of this invention may be prepared by directly dissolving taxol in the oil or by forming a first solution by dissolving taxol in a preliminary solvent such as an anhydrous alcohol followed by mixing with the oil and evaporation of the solvent.

The solutions of taxol or tumor-active analogs of taxol made by the methods of this invention are preferably used to prepare oil-in-water emulsions for pharmaceutical use in anti-tumor therapy. Emulsions are preferred vehicles for taxol for both intravenous and oral administration and can be prepared by any means known to the art using known surfactants and emulsion stabilizing components from the solutions of taxol in oils of this invention.

Oil-in-water emulsions containing taxol can also be made using self-emulsifying glasses prepared as disclosed in U.S. serial number 07/830,058 and subsequent related applications. Such glass compositions comprise a water-soluble, nonsurface active matrix compound and an oil containing solubilized taxol from which emulsions can be readily formed by contacting the glass with an aqueous phase. Melt-spinning technology as described in U.S. patents 5,011,532, 5,034,421 and can also be used to prepare colloidal dispersions for pharmaceutical administration of taxol.

Emulsions produced from self-emulsifying glasses or colloidal dispersions produced by melt-spinning technology do not require art-recognized surfactants or emulsifying agents.

A pharmaceutically effective emulsion containing taxol is produced from a self-emulsifying glass by mixing it with

sufficient aqueous phase to form an emulsion. No emulsive mixing or surfactants are necessary.

Emulsions and colloidal dispersions containing therapeutically effective amounts of taxol are administered to patients suffering from cancers against which taxol is known to have a therapeutic effect in appropriate oral or intravenous dosages to effect reduction in the disease.

Detailed Description of the Preferred Embodiments

A composition of matter is provided comprising a pharmaceutically effective amount of taxol or a tumor-active analog thereof solubilized in a pharmaceutically acceptable carrier comprising an oil having a dipole moment of between about 0.5 Debyes and about 2.0 Debyes, and preferably between about 1.6 and about 1.7 Debyes.

A pharmaceutically relevant dosage or pharmaceutically effective amount of taxol for humans is about 30 mg per dose, repeated several times at weekly intervals. As is well known in the art, the dosage employed will depend among other things upon the age, weight, and health status of the patient and upon the location and type of disease to be treated. At solubilities of taxol in present formulations and because of the toxicity of the Cremophor used in presently-available formulations, concentrations of only about 30 μg/ml are presently used to administer taxol. A volume of 1,000 ml is presently required for a single dose. High concentrations of taxol in oil, greater than or equal to about 1 mg/ml and typically between about 1 and about 10 mg/ml, are achievable through the use of this invention, thus allowing delivery of a pharmaceutically relevant dose in a significantly lower amount of the pharmaceutical preparation. Emulsions produced using the taxol solutions of this invention carry pharmaceutically effective amounts of taxol. Preferred emulsions carry from about 0.5 to 5 mg/ml of taxol, thus allowing delivery of the drug in up to one one-hundredth or less of the volume now used without toxic cosolvents or Cremophores.

Tumor-active analogs of taxol are known to the art and include analogs having acylated carbons of the taxene ring at the 7-position and 10-position. These taxol analogs can be solubilized at concentration levels similar to those of taxol in the oils of this invention.

Pharmaceutically acceptable oils are known to the art and include vegetable, flower, animal and marine oils. The oil used for solubilizing taxol is preferably a marine oil and, more preferably, a deep-water marine oil. Naturally occurring marine oils, deodorized marine oils, and processed marine oils are useful in this invention. Oils having ether lipid as a major component thereof are preferred. Ether lipids include glycerol ethers, saturated ethers, and polyunsaturated ethers. Oils containing terpene hydrocarbons as major components are also preferred. Terpene hydrocarbon oils are useful in the solutions and emulsions and pharmaceutical dosages of this invention. Terpene hydrocarbons from any source, including among others those isolated from natural sources, produced by processing of natural oils, and produced by synthesis are included in this invention.

Dipole moment measurements of various oils are readily available in the literature (e.g., McClellan, A.L. (1963) "Table of Experimental Dipole Moments," W.H. Freeman (publishers), San Francisco, CA; and Smith, J.W. (1955) "Electric Dipole Moments," Buttersworth Scientific Publications, London) and are experimentally determined by the method of oscillometry (Reilly, C.N. (1954) in New Instrumental Methods in Electrochemistry, P. Delahey (ed.), Interscience, New York, NY, pp. 319-345) or comparison to drug solubility (Groman, W.G. and Hol, G.D. (1964) Hol. J. Pharm. Sci. 53:1017).

The term oil is used herein to refer to substantially water-insoluble materials that are liquid at about room temperature or when slightly warmed. This definition excludes triacetin which is substantially water soluble.

The solutions of taxol or tumor-active analogs of taxol made by the methods of this invention are preferably used to prepare oil-in-water emulsions for pharmaceutical use in antitumor therapy. Emulsions are preferred vehicles for taxol for both intravenous and oral administration and can be prepared by any means known to the art using known surfactants from the solutions of taxol in oils of this invention. Surfactants useful in the preparation of such emulsions include, e.g., Pluronic F-86™ (BASF), polysorbate Tween 80™, those having HLB values between 10-13, and preferably Pluronic F-86™.

The taxol solutions, emulsions, colloidal dispersions and other pharmaceutical dosage forms of this invention can also comprise other pharmaceutically active agents so long as the solubility of taxol in the composition is not substantially decreased and the pharmaceutical activity of taxol is not substantially decreased. Taxol compositions of this invention can contain other ingredients which function to stabilize the emulsion, preserve the activity of the active ingredients, moderate pH or otherwise beneficially affect the composition for its intended application so long as the solubility of taxol and the activity of taxol is not substantially decreased.

Solutions of taxol or tumor-active taxol analogs in the pharmaceutically acceptable oils of this invention may be prepared by dissolving taxol crystals directly in the oil, preferably with the application of heat. More rapid dissolution is obtained by first dissolving the taxol in a more volatile, less viscous preliminary solvent such as anhydrous alcohol, e.g., ethanol or methanol. The primary solution is then mixed with an oil of this invention having a dipole moment of between about 0.5 and about 2.0 Debyes to form a second solution. This second solution may at this point be treated to remove the preliminary solvent, preferably by heating. Alternatively, the solvent may be removed later in the process as described below.

Solutions comprising taxol or a tumor-active taxol analog in a preferred oil can be emulsified by any means known to the art to form pharmaceutical compositions having concentrations of the tumor-active ingredient of at least about 0.1 mg/ml. Preerably the emulsions contain about 10% of the taxol solution in oil by weight. More useful emulsions of this invention have concentrations of the tumor-active ingredient equal to or greater than 0.5 mg/ml. Preferred emulsions contain from about 0.5 mg/ml to about 5 mg/ml. Emulsions comprising about 3 mg/ml are most preferred.

Mixtures of oils in which the mixture has a dipole moment between about 0.5 and 2.0 Debyes are useful for preparation of high concentration solutions of taxol or taxol-analogs.

Mixtures of oils in which the major component, i.e., greater than about 50% (v/v), is an ether lipid or in which the major component is a terpene hydrocarbon, such as squalene or squalane, are useful for preparation of high concentration solutions of taxol or taxol-analogs.

Oils in which taxol and taxol analogs are not soluble or are only poorly soluble can be included in compositions of this invention so long as the resulting oil mixture solubilizes greater than or equal to 1 mg/ml taxol or taxol-analog.

If preliminary solvent is present and if it is desired to remove it prior to adding matrix materials, preferred temperatures for removing the preliminary solvent from the taxol and oil solution are between about 50°C and about 70°C, preferably about 60°C. This step is preferably done by heating under a nitrogen blanket for a sufficient period to remove substantially all the solvent, typically about 20 minutes.

Pharmaceutical compositions of this invention include emulsions formed from taxol or taxol analog dissolved in oil

employing conventional methods and conventional pharmaceutical surfactants. Non-toxic surfactants are preferred.

This invention also includes self-emulsifying glasses prepared by the methods disclosed in U.S. serial number 07/830,058 filed February 3, 1992, incorporated herein by reference, and related applications. Such glass compositions comprise a water-soluble, nonsurface active matrix compound and an oil containing solubilized taxol or tumor-active taxol analog from which emulsions can be readily formed by contacting the glass with an aqueous phase. No emulsive mixing or art-recognized surfactants are required to form emulsions from such self-emulsifying glasses.

Emulsions and/or colloid dispersions comprising the taxol or taxol analog solutions of this invention can be formed using self-emulsifying glass technology as described in International Patent Application PCT 91/03864 and melt-spinning technology (described in U.S. Patents 5,011,532; 5,034,421 and 5,096,492).

A pharmaceutically effective emulsion containing taxol is produced from the self-emulsifying glass by mixing with sufficient aqueous phase, preferably an isotonic solution such as Normal Saline or 5% dextrose (D5W), to form an emulsion. No emulsive mixing or surfactants are necessary. The aqueous phase is added to the glass preferably at a ratio of between about 1 ml:1g, and about 5 ml:1g::aqueous phase:glass, to form compositions having a pharmaceutically-effective concentration of the tumor-active ingredient.

After storage for several hours without agitation, an emulsion prepared from a self-emulsifying glass has a particle size between about 5μm and about 1μm and remains stable at room temperature for periods of three weeks or more. Droplet size decreases over time. Droplet size of the emulsion as initially formed may be larger, e.g., between about 10μm and about 2μm.

Emulsions for therapeutic use containing greater than or equal to about 0.1 mg/ml and more preferably greater than or equal to about 0.5 mg/ml taxol or tumor-active taxol analog can be readily prepared by the foregoing methods and administered orally or intravenously.

Examples

Example 1: Taxol (Sigma T-7402), 4.0 mg, was dissolved in anhydrous methanol. The taxol solution was added to 0.400 ml squalane (Sigma S-4510, lot 88F3528). The methanol was then removed with heating under a nitrogen blanket at about 60°C for 10 minutes. The taxol was completely solubilized in the squalane oil.

Example 2: The taxol-in-oil solution of Example 1 was added to 1.62 g of sucrose in a 100 ml vacuum flask. Sufficient water to just dissolve the sucrose was added to the flask and the mixture was heated to 80°C in a rotary evaporator for approximately five minutes. Vacuum was applied to the flask at 500 mbar and continually increased to maintain bubbling. Vapor temperature was maintained no lower than 30°C. When the vapor temperature no longer increased, after about 30 minutes, maximum vacuum was applied and the flask lifted out of the water bath. The self-emulsifying glass product in the form of a foam was collected from the flask. The glass had a moisture content of less than or equal to 0.1% to less than or equal to 0.29%.

Example 3: The self-emulsifying glass of Example 2 was added to 0.8 ml normal saline and gently swirled by hand to produce an oil-in-water emulsion comprising taxol in the oil phase. Droplet size was measured to be about 2-10 μm.

Example 4: The emulsion of Example 3 was tested for therapeutic activity as follows:

Twelve mice weighing 14 to 25 grams, strain A/J (lung tumor model as described in Malkinson, A.M. (1920) Cancer Res. [suppl.]

52:2670s-2676s), having urethane-induced lung tumors, at an average of 30 per mouse after 14 weeks of treatment, are treated with the emulsion of Example 3 for a dosage of 5 mg/kg taxol. The emulsion is administered by bolus I.V. Treatment cycle is repeated four times. Controls using identical procedures and an equivalent oil/sucrose glass emulsion free of taxol are performed. At the end of the study, tumor number in the mice treated with the formulation of this invention is decreased significantly compared to controls.

CLAIMS:

1. A composition of matter comprising a pharmaceutically effective amount of taxol or a tumor-active analog thereof, solubilized in a pharmaceutically acceptable carrier comprising an oil having a dipole moment of between about 0.5 Debyes and about 2.0 Debyes.

2. The composition of claim 1 wherein said oil comprises an ether lipid as a major component.

3. The composition of claim 1 wherein said oil is a marine oil having an ether lipid as a major component thereof.

4. The composition of claim 1 wherein said oil comprises a terpene hydrocarbon as a major component.

5. The composition of claim 1 which comprises taxol.

6. An emulsion comprising the composition of claim 1.

7. The emulsion of claim 6 that is an oil-in-water emulsion.

8. A composition of matter comprising a pharmaceutically effective amount of taxol solubilized in an oil selected from the group consisting of orange roughy oil, shark liver oil, squalane and squalene.

9. The composition of claim 8 wherein said oil is squalane or squalene.

10. A composition of matter comprising an oil having a dipole moment of between about 0.5 Debyes and about 2.0 Debyes in which taxol or a tumor-active analog thereof is solubilized in said oil at a level greater than or equal to 1 mg/ml.

11. The composition of matter of claim 10 wherein said taxol or tumor-active analog thereof is solubilized in said oil at a level greater than or equal to 5 mg/ml.

12. The composition of matter of claim 11 wherein said oil is squalane or squalene.

13. A method for solubilizing taxol or a tumor-active taxol analog in a pharmaceutically acceptable carrier comprising:

(a) solubilizing taxol or said taxol analog in an anhydrous alcohol;

(b) mixing the solution of (a) with a sufficient amount of a pharmaceutically acceptable carrier comprising an oil having a dipole moment of between about 0.5 Debyes and about 2.0 Debyes, to solubilize said solution.

14. The method of claim 13 further comprising removing said anhydrous alcohol from the solution of step (b).

15. A pharmaceutical composition comprising the solution prepared by the method of claim 14.

16. The method of claim 14 further comprising preparing an oil-in-water emulsion with the solution from which said anhydrous alcohol has been removed.

17. An emulsion prepared by the method of claim 16.

18. A pharmaceutical dosage form comprising the composition of claim 1.

INTERNATIONAL SEARCH REPORT

Inte. onal Application No
PCT/US 93/09293

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K31/335 A61K9/107 A61K47/24 A61K47/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 107, no. 5, 3 August 1987, Columbus, Ohio, US; abstract no. 34441n, see abstract & GAMETE RES. vol. 17, no. 1 , 1987 pages 43 - 56 L.D.RUSSEL ET AL. 'Intratesticular injection as a method to assess the potential toxicity of various agents and to study mechanisms of normal spermatogenesis' ---	1
A	EP,A,0 118 316 (LIPID SPECIALITIES) 12 September 1984 see claims 18-21 see example 10 --- -/--	1-18

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 February 1994	[illegible]

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Scarponi, U

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 106, no. 22, 1 June 1987, Columbus, Ohio, US; abstract no. 182581c, & J.PARENTER.SCI.TECHNOL. vol. 41, no. 1 , 1987 pages 31 - 33 B.D.TARR ET AL. 'A new parenteral vehicle for the administration of some poorly soluble anti-cancer drugs' ---	1-18
A	JOURNAL OF THE NATIONAL CANCER INSTITUTE vol. 82, no. 15 , 1 August 1990 pages 1247 - 1259 E.K.ROWINSKY ET AL. 'Taxol:a novel investigational antimicrotubule agent' cited in the application Page 1251,left column:"Pharmaceutical data". -----	1-18

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ..ional Application No
PCT/US 93/09293

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0118316	12-09-84	US-A-	4534899	13-08-85
		CA-A-	1240692	16-08-88
		DE-A-	3474667	24-11-88
		JP-C-	1721376	24-12-92
		JP-B-	4007353	10-02-92
		JP-A-	59204198	19-11-84
		US-A-	4507217	26-03-85